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# Synthesis of (±)-phthalascidin 622

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A synthesis of functionalized phenolic α-amino-alcohols (±)-**8** and (±)-**16** as synthetic precursors of the catechol tetrahydroisoquinoline structure of phthalascidin 650 was disclosed. (±)-**8** was prepared in 5 steps from the commercially available sesamol. Starting from 3-methyl catechol **5**, 8 steps gave rise to the synthesis of phenolic α-amino-alcohol (±)-**16** in 27% overall yield. This synthetic strategy involved the elaboration of fully functionalized aromatic aldehyde **13** and its transformation into a phenolic α-amino-alcohol (±)-**16**, through a Knoevenagel condensation, simultaneous reduction of nitroketene and ester functions, and hydrogenolysis of the benzyl protecting group. The pentacycle (±)-**4** was obtained after 4 additional steps. The Pictet-Spengler cyclisation between the phenolic α-amino-alcohol (±)-**16** and the N-protected α-amino-aldehyde **4** allowed to obtain (1,3′)-bis-tetrahydroisoquinoline **17** with N-methylated and N-Fmoc removed. The last step was a Swern oxidation allowing the expected intramolecular condensation.

**phthalascidin, ecteinascidin, (1,3′)-bis-tetrahydroisoquinoline, Pictet-Spengler, Bishler-Napieralsky**

## 1 Introduction

The interest for the tetrahydroisoquinoline alkaloids is essentially aroused from their natural architectural complexity and their noteworthy biological properties as antitumor antibiotics [1]. The most active member of this family, Ecteinascidin 743 (**1**, Et 743), was isolated from the Caribbean tunicate *Ecteinascidia turbinate* [2–6] (Figure 1) and displayed highly potent cytotoxic activity against a variety of tumor cancer cells *in vitro* [7] and is approved for the teatment of soft tissue sarcoma under the brand name of Yondelis. The natural scarcity and potent medical use of Et 743 have attracted several groups to embark on its total synthesis [8–12]. With regard to the structural complexity of Et 743 and its relative unstability in solution, synthetic phthalascidins analogues were envisaged. Thus, the synthesis and biological evaluation of Pt 650 **2** was first reported by Corey *et al.* [13–16] and exhibited similar biological activity to the natural product. A semi-synthetic route was achieved by Cuevas *et al.* [17, 18] through fermentation of the bacteria *Pseudomonas fluorescens* to produce cyanosafracin B (**3**) [19], an antibiotic of bacterial origin. However, since the discovery of Pt 650, several research groups were involved in the research of potentially more active structures, bearing a piperazine system [20–35]. The most impressive results were reported by Myers, with the discovery of a quinaldic acid derivative (QAD, **3**), exhibiting excellent antitumoral activity against a range of cancer cell lines *in vitro* [20, 22]. This group also described the synthesis of a

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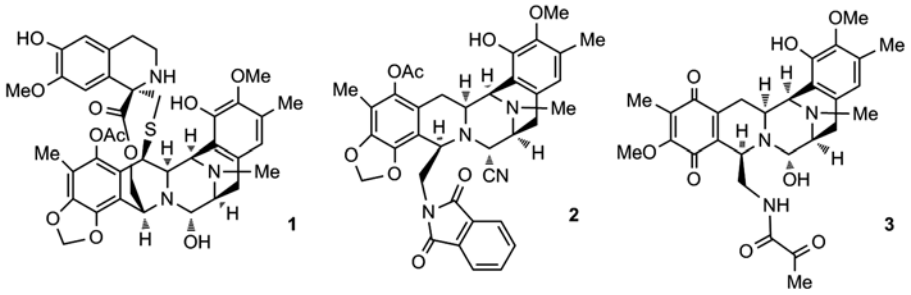


**Figure 1** Ecteinascidin 743 (**1**), Phthalascidin 650 (**2**) and Cyanosafracin B (**3**).

wide range of synthetic analogues using the solid supported chemistry [20, 21]. Spencer [23], Ong [24], Williams [25, 26], Liu [27, 28], Avendaño [29, 30], Echavarren [31], Kubo [32, 33] and Griecoer *et al.* [34] were also involved in the synthesis and biological evaluation of simpler Et 743 synthetic analogues and obtained promising results.

In our previous communications, our ongoing project concerning the synthesis and biological evaluation of Pt 650 synthetic analogues [36–38], encouraged us toward the synthesis of the iminobenzazocine pentacyclic system contained in the Pt 650 starting from 3-methylcatechol **5** and sesamol **6**.

Herein, we report an efficient synthesis of the tetrahydroisoquinoline alkaloid (±)-phthalascidin 622 **4** (Figure 2) by Pictet-Spengler condensation involving N-protected α-amino-alcohol **12** and aminoalcohol **16**. After suitable modifications (nitrogen methylation and Fmoc deprotection, Swern oxidation), an intramolecular Strecker cyclisation from the 1,3′-bistetrahydroisoquinoline **17** could give rise to the formation of a (±)-Pt 650 analogue containing a methoxy group in place of the classical acetoxy group. As far as we know, the synthesis of this 16-[(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)methyl]-6,6a,7,13,14,16-hexahydro-8-hydroxy-5,9-dimethoxy-4,10,17-trimethyl-7,13-Imino-12*H*-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine (phthalascidin 622 (**4**)) was never described in literature, although its antitumor efficiency has already been evaluated by Corey *et al.* [9].

## 2 Experimental

Starting materials were obtained from commercial suppliers and used without further purification. Solvents were distilled prior to use. Flash chromatographic purification was carried out on 230–400 mesh silica gel 60. NMR spectra were recorded on DRX 300 and 500 Brücker FT spectrometers. Abbreviation was used as: s (singlet), d (doublet), dd (divided doublet), t (triplet), q (quadruplet), m (multiplet).

*5-Methoxybenzo[d][1,3]dioxole-5-carbaldehyde (7) [39]*

To a stirring solution of sesamol **5** (25 g, 181 mmol) in acetone (400 mL) under Ar, was added $K_2CO_3$ (87.5 g, 633.5 mmol) and MeI dropwise (51.3 g, 362 mmol). The mixture was then stirred at room temperature for 24 h. The reaction mixture was filtered off and the solid washed with $Et_2O$ (3× 100 mL). The organic layer was washed successively with 1.5 N HCl (50 mL) and 1 N NaOH (50 mL), dried over $MgSO_4$ and evapored. To a solution of 5.32 g of the pure 5-methoxybenzo[d][1,3]dioxole (35.11 mmol) in dry THF (21 mL), 2.5 M *n*-BuLi (35 mL, 86 mmol) in hexane was added at –20 °C. The mixture was stirred for 1 h, and then MeI (14.8 g, 105.34 mmol) in THF (21 mL) was added

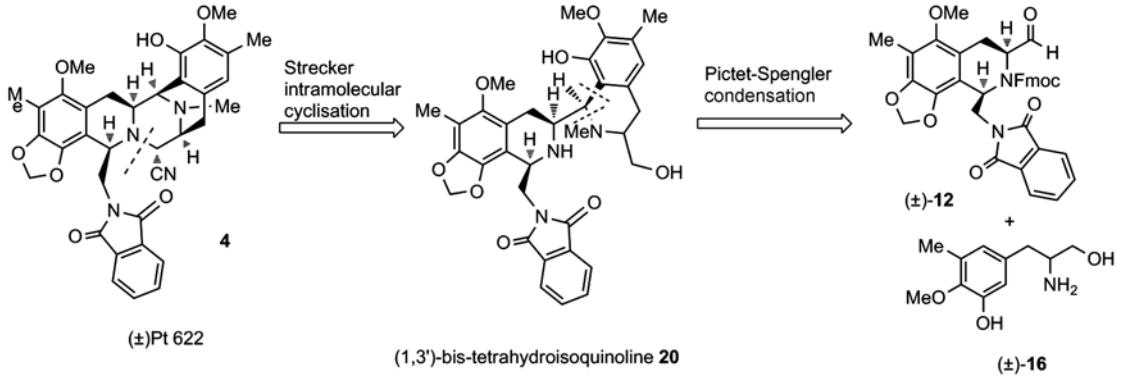



**Figure 2** Retrosynthetic analysis of Phthalascidin 622.

dropwise. After stirring for an additional time of 1 h, $H_2O$ (100 mL) was added. The mixture was then extracted with ether (3 × 100 mL). The organic layers were washed with 1 N NaOH (150 mL), dried over $MgSO_4$ and evapored. The crude residue was purified by flash column chromatography (silica gel, cyclohexane) to give the 5-methoxybenzo[d][1,3] dioxole intermediate (5.17 g, 89%). This compound (5 g, 30.1 mL) was dissolved in DMF and added to a solution of $POCl_3$ (4.2 mL, 45.2 mmol) preliminary added dropwise at 0 °C to a stirred anhydrous DMF (10 mL). The mixture was stirred at 100 °C for 3 h. Then a saturated $NaHCO_3$ aqueous solution (100 mL) was added at 0 °C and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The organic layers were dried over $MgSO_4$ and evaporated. The residue was recrystallized from *n*-heptane to give **7** as colourless crystals (5.78 g, 85%). Mp 95–96 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.19 (s, 1H, CHO), 7.11 (s, 1H, ArH), 6.03 (s, 2H, $OCH_2O$), 3.84 (s, 3H, $OCH_3$), 2.19 (s, 3H, $CH_3$). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 188.9, (CHO), 160.4, 153.0, 144.5, 123.5, 103.5 (ArC), 114.0 (ArCH), 102.5 ($CH_2$), 64.6 ($OCH_3$), 9.1 ($CH_3$). ESI-MS: *m/z* (%) = 194 $[M]^+$ (100), 163 $[M–CH_3OH]^+$ (21), 148 $[M–OCH_3\text{-}CH_2]^+$ (54). Anal. calcd for $C_{10}H_{10}O_4$: C 61.85; 5.19%, found C 62.00; 5.25%.

*(±)-2-Amino-3-(6-methoxy-7-methylbenzo[d][4,5]dioxol-5-yl) propan-1-ol (**8**) [40]*

To a srirring solution of $TiCl_4$ (2.93 g, 15.46 mmol) in THF (10 mL), **7** (0.5 g, 2.58 mmol) in THF (4.5 mL) was added dropwise at −5 °C. After stirring at room temperature for 1h, ethyl nitroacetate (0.595 g, 5.66 mmol) was added at −5 °C. Then, the mixture was stirred for an additional time of 1 h and *i*-$Pr_2$NEt (2.98 g, 23.17 mmol) was added. The mixture was then stirred at room temperature for 24 h and $H_2O$ (20 mL) was added. The residue was extracted with $CH_2Cl_2$ (3 × 50 mL). The organic layer was washed with brine, dried over $MgSO_4$, evaporated and purified by flash chromatography (silica gel, cyclohexane/AcOEt) to yield a 50:50 mixture of (*E*):(*Z*) of the corresponding olefine as a yellow oil (0.79 g, 99%). Then, olefin intermediate (0.5 g, 1.618 mmol) was reduced with $LiAlH_4$ (614.2 mg, 16.18 mmol) in $Et_2O$ (30 mL), under Ar. After stirring at room temperature for 4 h, $CH_2Cl_2$ (50 mL), $H_2O$ (0.62 mL), 2N NaOH (0.62 mL) and $H_2O$ (1.86 mL) were added at 0 °C until a white solid appeared. The mixture was then filtered and the solid washed with $CH_2Cl_2$, dried over $MgSO_4$, and evaporated to yield 8 as a pale yellow oil (352 mg, 91%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.47 (s, 1H, ArH), 5.87 (s, 2H, $OCH_2O$), 4.55 (s, 1H, OH), 3.63 (s, 3H, $OCH_3$), 3.49 (dd, 1H, *J* = 11.0, 4.1 Hz, $CH_2O$), 3.33 (dd, 1H, *J* = 11.0, 6.0 Hz, CH2O), 2.99 (s, 1H, CHN), 2.64 (m, 1H, $CH_2CHN$), 2.50 (m, 1H, $CH_2CHN$), 2.7 (br s, 2H, $NH_2$), 2.13 (s, 3H, $CH_3$). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 151.7, 145.4, 143.1, 123.5, 113.5, 107.0 (ArC), 101.1 ($CH_2$), 66.05 ($CH_2$), 61.01 ($OCH_3$), 53.98 (CH), 34.75 ($CH_2$), 9.47 ($CH_3$). ESI-MS: *m/z* (%) = 240 $[M + H]^+$ (100), 179 $[M–H_3NCHCH_2OH]^+$ (68). Anal. calcd for $C_{12}H_{17}O_4N$ C 60.24;H 7.16; 5.85%, found C 60.11; H 6.98; N 5.73%.

*(9-((1,3-Dioxoisoindolin-2-yl)methyl)-3-(6-methoxy-4-methyl-6,7-dihydro-[1,3]dioxolo[4,5-h]isoquinolin-7-yl)methyl-2-(1,3-dioxoisoindolin-2-yl)acetate (**9**)*

To a stirring solution of **8** (0,58 g, 2.43 mmol) in $CH_2Cl_2$ (42 mL) was added $Et_3N$ (0.49 g, 4.85 mmol) and phthalylglydyl chloride (1.30 g, 5.82 mmol) at 0 °C. The mixture was stirred 3 h at room temperature. The solution was then washed with 1.5 N HCl (10 mL), aqueous $Na_2CO_3$ (30 mL), brine, dried over $Na_2SO_4$, evaporated and purified by flash column chromatography (silica gel, cyclohexane/EtOAc, 94%). To the pure 2-(2-((1,3-dioxoisoindolin-2-yl)acetamido)-3-(6-methoxy-7-methylbenzo[d][1,3]dioxol-5-yl)propyl-2-(1,3-dioxoisoindolin-2-yl)acetate (1.30 g, 2.12 mmol) in $CH_3CN$ (2.62 mL) was added dropwise $POCl_3$ (0.975 g, 6.36 mmol) at 0 °C and stirred and heated at 90 °C for 3 h. The reaction mixture was neutralized with a saturated $Na_2CO_3$ aqueous solution (15 mL) at 0 °C and the aqueous layer was extracted with $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$, evaporated and purified by flash chromatography (silica gel, cyclohexane/AcOEt = 50:50 to 0:100) to yield **9** as a white solid (1.19 g, 95%). Mp 110–112 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.92 (m, 2H, *J* = 5.4, 3.0 Hz, 2ArH), 7.89 (m, 2H, *J* = 5.4, 3.0 Hz, 2ArH), 7.76 (m, 4 ArH), 6.07 (d, 2H, *J* = 16.2 Hz, $OCH_2O$), 5.13 (dd, 1H, *J* = 17.6, 2.8 Hz, $NCCH_2N$), 4.78 (d, 1H, *J* = 17.7 Hz, $NCCH_2N$), 4.42 (d, 1H, *J* = 17.7 Hz, $OCOCH_2N$), 4.35 (d, 1H, *J* = 17.4 Hz, $OCOCH_2N$), 4.29 (m, 1H, *J* = 10.7, 4.7 Hz, $CH_2OCO$), 4.12 (m, 1H, *J* = 10.7, 8.0 Hz, $CH_2OCO$), 3.67 (s, 3H, $CH_3$), 3.57 (m, 1H, CHN), 2.93 (d, 1H, *J* = 15.8 Hz, $CH_2CHN$), 2.28 (m, 1H, $CH_2CHN$), 2.23 (s, 3H, $CH_3$). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 168.9 (CO), 167.7 (NCO), 167.3 (CN), 150.4, 146.2, 141.8, 132.8, 132.4, 121.0, 115.9 (ArC), 134.6, 134.2, 124.0, 123.7 (ArCH), 102.0 ($OCH_2O$), 68.9 (CH2), 61.2 ($OCH_3$), 55.5 (CH), 43.5 ($CH_2$), 39.1 ($CH_2$), 22.7 (CH2), 9.9 ($CH_3$). ESI-MS: *m/z* (%) = 596 $[M + H]^+$ (100). HRMS (ESI) calcd for $C_{32}H_{26}O_9N_3$ $[M + H]^+$ 596.1669, found 596.1670.

*(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)acetic acid 9-(1,3-dioxo-1,3-dihydroisoindol-2-yl-methyl)-5-methoxy-4-methyl-6,7,8,9-tetrahydro-[1,3]dioxolo[4,5-h]isoquinolin-7-yl-methyl ester (**10**)*

A mixture of **9** (1 g, 1.68 mmol) and 10% Pd/C (0.358 mg, 0.337 mmol) in MeOH/$CH_2Cl_2$ (1:1.5 mL) was stirred for 24 h at room temperature under $H_2$ atmosphere (10 bars). Then, the residue was filtered through Celite, and dried over $Na_2SO_4$, evaporated and purified by flash chromatography (silica gel, cyclohexane/AcOEt 7:3) to yield **10** as a colourless solid (0.812 g, 81%). Mp 180 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.91 (m, 4H, 4ArH), 7.78 (dd, 2H, *J* = 5.5, 3.0 Hz, 2ArH), 7.75 (dd, 2H, *J* = 5.5, 3.0 Hz, 2ArH), 5.92 (s, 1H,

$OCH_2O$), 5.88 (s, 1H, $OCH_2O$), 4.60 (m, 1H, $CHCH_2N$), 4.52 (s, 1H, $OCOCH_2N$), 4.51 (s, 1H, $OCOCH_2N$), 4.45 (dd, 1H, $J$ = 14.0, 4.3 Hz, $CHCH_2N$), 4.23 (m, 2H, $CH_2OCOCH_2$), 3.86 (dd, 1H, $J$ = 14.0, 8.9 Hz, $CHCH_2N$), 3.77 (s, 3H, $OCH_3$), 2.87 (dd, 1H, $J$ = 15.6, 2.8 Hz, $CH_2CHN$), 2.35 (m, 1H, $CH_2CHN$), 2.17 (s, 3H, $CH_3$). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 169.2 (CO), 167.8, 167.6 (NCO), 151.3, 144.9, 140.0, 132.5, 132.4, 121.4, 115.4, 112.6 (ArC), 134.7, 134.6, 124.0, 123.0 (ArCH), 101.2 ($OCH_2O$), 69.4, 42.7, 39.3, 27.1 ($CH_2$), 60.9 ($OCH_3$), 52.6, 51.7 (CH), 9.5 ($CH_3$). ESI-MS: *m/z* (%) = 598 $[M + H]^+$ (100). HRMS (ESI) calcd for $C_{32}H_{27}O_9N_3$ $[M+H]^+$ 598.1826, found 598.1825.

*(±)-N-Fmoc-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)acetic acid 9-(1,3-dioxo-1,3-dihydroisoindol-2-yl-methyl)-5-methoxy-4-methyl-6,7,8,9-tetrahydro-[1,3]dioxolo[4,5-h]isoquinolin-7-yl-carbaldehyde (**12**)*

A 15% by weight solution of Dess-Martin periodinane (670 mg, 0.237 mmol) in $CH_2Cl_2$ was added to a solution of the *N*-Fmoc α-amino-alcohol preliminary obtained from (±)-**11** (100 mg, 0.158 mmol) in $CH_2Cl_2$ (1 mL) at 0 °C. After stirring for 30 min at room temperature, the mixture was diluted with $Et_2O$ (10 mL), and saturated solutions of $Na_2S_2O_3$ (5 mL) and $NaHCO_3$ (5 mL) were added. The resulting biphasic mixture was then stirred for 30 min, by which time both layers had become clear and colourless. After 20 min under stirring, the mixture was diluted with $Et_2O$ (10 mL), and the organic layer separated, washed successively with $NaHCO_3$ (10 mL), $H_2O$ (10 mL) and brine (10 mL), dried over $Na_2SO_4$, filtered, evaporated and purified by flash column chromatography ($SiO_2$, cyclohexane/AcOEt = 80/20) to yield (±)-**12** as a white solid (79.7 mg, 80%). Mp 114 °C. $R_f$ = 0.6 (cyclohexane/AcOEt = 50/50). $^1$H NMR (500 MHz, DMSO-$d_6$, 80 °C) $\delta$ 9.57 (s, 1H, C*H*O), 7.84 (s, 6H, 6Ar*H*), 7.60 (br s, 1H, 1Ar*H*), 7.51 (d, 1H, $J$ = 7.6 Hz, 1Ar*H*), 7.41–7.37 (m, 2H, 2Ar*H*), 7.31–7.27 (m, 2H, 2Ar*H*), 5.91 (s, 1H, $OCH_AH_BO$), 5.64 (t, 1H, $J$ = 7. 2 Hz, $CHCH_2N$), 5.44 (s, 1H, $OCH_AH_BO$), 4.24 (m, 2H, $OCH_AH_BCH$ and $OCH_AH_BCH$), 4.16 (m, 1H, $OCH_2CH$), 4.05 (m, 1H, CHCHO), 3.93 (m, 1H, $CHCH_AH_BN$), 3.87 (m, 1H, $CHCH_AH_BN$), 3.66 (s, 3H, $OCH_3$), 3.14 (m, 1H, $J$ = 5.6, 15.4 Hz, $CH_AH_BCHN$), 2.86 (dd, 1H, $J$ = 11.7, 15.4 Hz, $CH_AH_BCHN$), 2.09 (s, 3H, $CH_3$). $^{13}$C NMR (125 MHz, DMSO-$d_6$, 80 °C) $\delta$ 199.5 (*C*HO), 167.0 (3C, 3NCO), 155.3 (ArCO), 149.9 (Ar*C*O), 144.2 (Ar*C*O), 143.2 (ArC), 140.3 (2ArC), 138.7 (ArC), 134.1 (2Ar*C*H), 131.1 (2ArC), 127.3 (2Ar*C*H), 126.7 (2Ar*C*H), 124.4 (2Ar*C*H), 122.6 (2Ar*C*H), 119.6 (2Ar*C*H), 117.0 (ArC), 112.5 (ArC), 112.1 (ArC), 100.9 ($OCH_2O$), 66.2 ($CH_2$), 60.4 (CH and $OCH_3$), 48.1 (CH), 46.3 (CH), 41.5 ($CH_2$), 20.7 ($CH_2$), 8.5 ($CH_3$). ESI-MS: *m/z* (%) = 653 $[M+Na]^+$ (33), 631 $[M + H]^+$ (69), 453 $[M + H–C_{13}H_9CH_2]^+$ (41), 409 $[M + H–C_{13}H_9CH_2–CO_2]^+$ (100), 391 $[M + H–C_{13}H_9CH_2–CO_2–H_2O]^+$ (100). HRMS (ESI) calcd for $C_{37}H_{30}N_2NaO_8$ $[M+Na]^+$ 653.1900, found 653.1901.

*3-(Benzyloxy)-4-methoxy-5-methylbenzaldehyde (**13**)*

To a solution of **5** (3.8 g, 15.74 mmol) in DMF/acetone 2/1 (50 mL) were added $K_2CO_3$ (6.55 g, 47.34 mmol) and BnBr (3 g, 17.52 mmol). After stirring at room temperature for 2 h, the reaction mixture was filtered and the solid washed with $Et_2O$ (400 mL). The organic layer was washed with a 1.5 N HCl solution (100 mL). Then, the residue was extracted with $Et_2O$ (3 × 150 mL), dried over $MgSO_4$, evaporated and purified by flash column chromatography (silica gel, cyclohexane/ethyl acetate = 8:2) to yield the corresponding 4-hydroxy-3-benzyloxy-5-methylphenol as an orange oil (5.5 g, 90%). This intermediate (5 g, 30.12 mmol) in AcOH (150 mL) and HMTA (10.54 g, 75.3 mmol) was stirred at 100 °C for 96 h. After this period, the solution was cooled and a saturated solution of $NaHCO_3$ was added. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The organic layers were dried over $MgSO_4$, evaporated and purified by flash column chromatography (silica gel, cyclohexane) to give the corresponding 3-(benzyloxy)-4-hydroxy-5-methylbenzaldehyde in 90% yield (4.97 g), $R_f$ = 0.3 (cyclohexane/AcOEt = 9:1. To a solution of pure 3-(benzyloxy)-4-hydroxy-5-methylbenzaldehyde (38.1 g, 0.196 mmol) in acetone (212 mL) were added $K_2CO_3$ (81.4 g, 0.589 mmol) and $Me_2SO_4$ (49.5 g, 0.393 mmol). After stirring at room temperature for 4 h, the reaction mixture was filtered and the solid washed with $Et_2O$. The organic layer was washed with a 1.5 N HCl solution (180 mL) and 1 N NaOH solution (200 mL). Then, the residue was extracted with $Et_2O$, dried over $MgSO_4$, evaporated and purified by flash column chromatography (silica gel, cyclohexane/AcOEt = 100:2→95:5) to yield **13** as a pale yellow oil (35.8 g, 88%). $R_f$ = 0.6 (cyclohexane/ACOEt = 9:1). $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 9.75 (s, 1H, C*H*O), 7.20 (s, 1H, ArH), 7.19 (s, 1H, ArH), 4.56 (sept, 1H, $J$ = 6.0 Hz, $CH(CH_3)_2$), 3.82 (s, 3H, $OCH_3$), 2.22 (s, 3H, $CH_3$), 1.31 (d, 6H, $J$ = 6.0 Hz, CH ($CH_3)_2$). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 191.8 (*C*HO), 154.2 (Ar*C*), 151.5 (Ar*C*), 133.0 (Ar*C*H), 132.3 (Ar*C*H), 127.1 (Ar*C*), 112.1 (Ar*C*), 71.2 ($CH(CH_3)_2$), 60.5 ($OCH_3$), 22.4 ($CH(CH_3)_2$), 16.4 ($CH_3$). EI-MS: *m/z* (%) = 208 $[M]^+$ (36), 166 $[M–C_3H_6]^+$ (100), 165 $[M–C_3H_7]^+$ (56), 151 $[M–CH_3–C_3H_6]^+$ (30), 123 $[M–C_3H_6–CH_3–CO]^+$ (22). Anal. calcd for $C_{12}H_{16}O_3$ C 69.21; H 7.74 %, found C 69.03; H 7.93 %.

*2-Amino-3-(3-(benzyloxy)-4-methoxy-5-methylphenyl)propan-1-ol (**15**)*

To a stirring solution of $TiCl_4$ (2.66 g, 14.04 mmol) in THF (9 mL) was added dropwise at −5 °C **13** (0.6 g, 2.34 mmol) contained in THF (4.1 mL). After stirring at room temperature for 30 min, ethyl nitroacetate (0.685 g, 5.15 mmol) was added at −5°C. Then, the mixture was stirred for an additional time of 30 min nd *i*-$Pr_2NEt$ (2.76 g, 21.09 mmol) was added. The mixture was then stirred at room temperature, stirring for 24 h and $H_2O$ (20 mL) was added. The residue was extracted with $CH_2Cl_2$ (3 × 50 mL). The organic layers

were washed with brine, dried over $MgSO_4$, evaporated and purified by flash column chromatography ($SiO_2$, cyclohexane/AcOEt = 100:0→90:10) to yield a 40:60 mixture of **14** as a yellow oil (0.64 g, 74 %). Nitroesters **14** (0.2 g, 0.539 mmol) was then reduced with $LiAlH_4$ (0.205 g, 5.39 mmol) in a stirring solution of $Et_2O$ (12 mL), under an atmosphere of argon. After stirring at room temperature for 4 h, $CH_2Cl_2$ (25 mL), $H_2O$ (0.2 mL), 2N NaOH (0.2 mL) and $H_2O$ (0.6 mL) were added at 0 °C until a white solid appears. The mixture was then filtered and the solid washed with $CH_2Cl_2$ (3 × 30 mL). The filtrate was dried over $Na_2SO_4$, evaporated to yield **15** as a pale yellow oil (151 mg, 93%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.48 (d, 2H, $J$ = 7.23 Hz, ArH), 7.42 (m, 2H, ArH), 7.35 (m, 1H, $J$ = 7.3 Hz, ArH), 6.66 (s, 1H, ArH), 6.65 (s, 1H, ArH), 5.14 (s, 2H, $CH_2$), 3.87 (s, 3H, $CH_3$), 3.61 (dd, 1H, $J$ = 10.8, 3.8 Hz, C$H_A$H$_B$), 3.38 (dd, 1H, 10.8, 7.0 Hz, CH$_A$$H_B$), 3.08 (m, 1H, CH), 2.94 (m, 1H, OH), 2.7 (dd, 1H, $J$ = 13.6, 5.1 Hz, C$H_C$H$_D$), 2.43 (m, 1H, CH$_A$$H_B$), 2.29 (s, 3H, $CH_3$ ), 2.26 (br s, 21H, $NH_2$). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 152.0 (Ar*C*O), 147.0 (Ar*C*O), 137.6 (Ar*C*), 134.3 (Ar*C*), 132.5 (Ar*C*), 128.9 (2C, ArC*H*), 128.3 (ArC*H*), 127.7 (2C, ArC*H*), 124.3 (ArC*H*), 113.5 (ArC*H*), 71.1 ($CH_2$), 66.7 ($CH_2$), 60.6 ($OCH_3$), 54.5 (CH), 40.9 ($CH_2$), 16.3 ($CH_3$). ESI-MS: *m/z* (%) = 302 $[M + H]^+$ (100), 272 $[M + H–CH_3OH]^+$ (21), 241 $[M + H–H_3NCHCH_2OH]^+$ (13). HRMS (ESI) calcd for $C_{18}H_{23}NO_3Na$ $[M+Na]^+$ 324.1576, found 324.1577. Anal. calcd for $C_{18}H_{23}NO_3$: C 71.73, H 7.69, N 4.65%, found C 71.54, H 7.80, N 4.52%.

*(±)-5-(2-Amino-3-hydroxypropyl)-2-methoxy-3-methylphenol (**16**) [41]*

A mixture of **15** (0.16 g, 0.532 mmol) and 10% Pd/C (64 mg), in 1:1 mixture of MeOH/$CH_2Cl_2$ (9 mL), was stirred overnight at room temperature under 5 bars of $H_2$ atmosphere. After the catalyst was filtered and washed with MeOH, the filtrate was dried over $Na_2SO_4$ and evaporated to give **16** as a colourless oil (110 mg, 98%). $^1$H NMR ($CD_3OD$, 500 MHz) $\delta$ 6.65 (d, 1H, $J$ = 1.9 Hz, Ar*H*), 6.6 (d, 1H, $J$ = 1.0 Hz, Ar*H*), 4.93 (s, 4H, $NH_2$, ArCOH, OH), 3.77 (s, 3H, $OCH_3$), 3.71 (m, 1H, OC$H_A$H$_B$), 3.53 (dd, 1H, $J$ = 11.7, 1.3 Hz, OCH$_A$$H_B$), 3.39 (br, 1H, CH), 2.79 (d, 2H, $J$ = 7.5 Hz, C$H_2$CHN), 2.25 (s, 3H, $CH_3$). $^{13}$C NMR (MeOH, 125 MHz) $\delta$ 150.4 (Ar*C*O), 145.5 (Ar*C*O), 132.1 (Ar*C*), 132.0 (Ar*C*), 122.5 (Ar*H*), 115.0 (Ar*H*), 60.9 ($OCH_2$), 59.4 ($OCH_3$), 54.8 (CH), 35.3 (*C*$H_2$CHN), 15.0 ($CH_3$). ESI-MS: *m/z* (%) = 212 $[M + H]^+$ (100), 151 $[M + H–H_3NCHCH_2OH]^+$ (40). HRMS (EI) calcd for $C_{11}H_{17}O_3N$ $[M]^+$ 211.1208, found 212.1207.

*(7S,9R)-(9H-Fluoren-9-yl)methyl 9-((1,3-dioxoisoindolin-2-yl)methyl)-7-((1R,3S)-8-hydroxy-3-(hydroxymethyl)-7-methoxy-2,6-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-5-methoxy-6,7-dihydro-[1,3] dioxolo[4,5-h]isoquinoline-8(9H)-carboxylate (**17**)*

A mixture of aldehyde **12** (550 mg, 0.873 mmol) and (±)-5-(2-amino-3-hydroxypropyl)-2-methoxy-3-methylphenol **16** (368 mg, 1.74 mmol) in 7:3 mixture of toluene/TFA (4.7 mL), was stirred overnight at 80 °C. Then, the reaction mixture was neutralized with a saturated $Na_2CO_3$ aqueous solution (15 mL) at 0 °C and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 100 mL). The organic layers were dried over $Na_2SO_4$, evaporated and purified by flash column chromatography (silica gel, cyclohexane/AcOEt = 90:10→40:60) to yield the regioisomers **17** and **18**, bis-1,3′-tetrahydroisoquinolines as a brown oil. **17** (210 mg, 33%), $R_f$ = 0.3, **18** (130mg, 18%), $R_f$ = 0.2 (cyclohexane/AcOEt = 50/50). $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.80 (m, 2H, 2ArH), 7.7 (m, 4H, 4ArH), 7.53 (m, 1H, 1ArH), 7.35 (m, 3H, 3ArH), 7.26 (s, 2H, 2ArH), 6,50 (s, 1H, ArH), 6.35 (m, 1H, C*H*CH$_2$N), 6.22 (s, 1H, OC$H_A$H$_B$O), 5.96 (m, 1H, C*H*CHCN), 5.84(s, 1H, OCH$_A$$H_B$O), 5.65 (s br, 2H, OH and NH), 5.56 (s, 1H, ArOH), 5.11 (m, 1H, C*H*CH$_2$O) 4.57 (d, 1H, $J$ = 6.4 Hz, CHC*H*CN), 4.22 (m, 2H, OC$H_A$H$_B$CH and OCH$_A$$H_B$CH), 4.04 (m, 2H, CHC$H_2$N), 3.76 (s, 6H, 2$OCH_3$), 3.73 (m, 2H, OC$H_A$H$_B$ and OCH$_A$$H_B$), 3.57 (m, 1H, CH), 3.46 (m, 2H, C$H_2$CHN), 2.54 (m, 1H, C$H_A$H$_B$CHN ), 2.26 (s, 3H, $CH_3$), 2.21 (m, 1H, CH$_A$$H_B$CHN), 2.08 (s, 3H, $CH_3$).

*(7S,9R)-(9H-Fluoren-9-yl)methyl 9-((1,3-dioxoisoindolin-2-yl)methyl)-7-((1R,3S)-8-hydroxy-3-(hydroxymethyl)-7-methoxy-2,6-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-5-methoxy-4-methyl-6,7-dihydro-[1,3]dioxolo[4,5-h]isoquinoline-8(9H)-carboxylate (**19**)*

**17** (110 mg, 0.13mmol) was dissolved in 8:9 mixture of $CH_2O$/$HCO_2H$ (1.7 mL) and stirred under atmosphere of argon at 70 °C. After 23 h the reaction mixture was basified with $NaHCO_3$ (100 mL) aqueous solution at 0 °C, extracted with DCM. The combined organic layers were dried over $Na_2SO_4$, filtered, evaporated and purified by flash column chromatography ($SiO_2$, cyclohexane/80:20→50:50) to give rise the protected amine 19 (95 mg, 62%). $R_f$ = 0.6 (cyclohexane/ACOEt = 5:5). $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.80 (m, 4H, 4Ar*H*), 7.70 (m, 2H, 2ArH), 7.58 (m, 1H, ArH), 7.49 (m, 2H, ArH), 7.41 (m, 2H, ArH), 7.26 (s, 1H, ArH), 6,55 (s, 1H, ArH), 6.06 (m, 1H, C*H*CH$_2$N), 5,66 (s, 1H, OC$H_A$H$_B$O), 5.46 (s, 3H, $NCH_3$), 4.90 (s, 1H, OCH$_A$$H_B$O), 4.70 (s br, 1H, ArOH), 4.65 (s br, 1H, OH), 4.45 (m, 1H, C*H*CHCN) 4.42 (m, 1H, C*H*CH$_2$O), 4.19 (m, 1H, OC$H_A$H$_B$CH) 4.13 (m, 1H, OCH$_A$$H_B$CH), 4.08 (d, 1H, $J$ = 6.4 Hz, CHC*H*CN), 3.98 (m, 2H, CHC$H_2$N), 3.82 (s, 3H, $OCH_3$), 3.57 (s, 3H, $OCH_3$), 3.45 (m, 2H, OC$H_A$H$_B$ and OCH$_A$$H_B$), 3.23 (m, 1H, CH), 2.90 (m, 1H, C$H_A$H$_B$N), 2.60 (m, 1H, CH$_A$$H_B$CHN), 2.35 (m, 1H, C$H_C$H$_D$CHN ), 2.27 (s, 3H, $CH_3$), 2.17 (m, 1H, CH$_C$$H_D$CHN), 2.01 (s, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 167.6 (NCO), 157.2 (NCO), 150.4 (ArC), 150.0 (ArC), 146.8 (ArC), 144.7 (ArC), 143.6 (ArC), 141.4 (ArC), 141.2 (ArC), 139.3 (ArC), 137.6 (ArC), 133.9 (Ar*C*H), 132.4 (Ar*C*H), 131.8 (Ar*C*H), 131.3 (ArC), 130.5 (ArC), 130.0 (Ar*C*H), 128.2 (2Ar*C*H), 128.1 (2Ar*C*H),

127.8 (ArC), 127.7 (Ar*C*H), 127.2 (ArC), 125.5 (ArC), 123.2 (Ar*C*H), 120.3 (ArC), 120.0 (Ar*C*H), 119.9 (Ar*C*H), 114.2 (Ar*C*H), 113.1 (ArC), 112.8 (ArC), 100.9 ($OCH_2O$), 69.0 (CH), 63.8 ($OCH_2$), 63.7 ($CH_2$),61.1 ($OCH_3$), 59.9 ($NCH_3$, $OCH_3$ ), 47.8 (2CH), 47.1 (CH), 39.8 ($CH_2$ ), 31.8 ($CH_2$ ), 26.8 ($CH_2$ ), 15.8 ($CH_3$), 9.0 ($CH_3$). ESI-MS: *m/z* (%) = 838 $[M + H]^+$ (100), 837 $[M + 2H]^+$ (51).

*2-(((7S,9R)-7-((1R,3S)-8-Hydroxy-3-(hydroxymethyl)-7-methoxy-2,6-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-5-methoxy-4-methyl-6,7,8,9-tetrahydro-[1,3]dioxolo[4,5-h]isoquinolin-9-yl)methyl)isoindoline-1,3-dione (**20**)*

To a solution of **19** (210 mg, 0.25 mmol) in DCM (0.84 mL) was added DBU (49 μL) under atmosphere of argon. After stirring at room temperature for 30 min, the reaction mixture was dissolved in DCM (20 mL) and washed respectively with water and brine. The organic layer was then dried over $Na_2SO_4$, filtered, evaporated and purified by flash column chromatography ($SiO_2$, DCM/ MeOH 100:00 →90:10) to give **20** as a brown solid (150 mg, 97%). $R_f$ = 0.5 (DCM/MeOH = 90:10). $^1$H NMR ($CDCl_3$ , 500 MHz) $\delta$ 7.84 (dd, 1H, $J$ = 5.4, 3.0 Hz, ArH), 7.74 (dd, 1H, $J$ = 5.5, 3.0 Hz, ArH), 7.70 (dd, 1H, $J$ = 5.4, 3.0 Hz, ArH), 7.68 (dd, 1H, $J$ = 5.4, 3.1 Hz, ArH), 7.26 (s, 1H, ArH), 6.65 (d, 1H, $J$ = 9.3 Hz, $OCH_AH_BO$), 5.83 (d, 1H, $J$ = 16.6 Hz, $OCH_AH_BO$), 5.82 (s, 1H, ArOH), 4.59 (m, 1H, $CHCH_2N$), 4.51 (s br, 1H, OH), 4.4 (m, 1H, $CHCH_AH_BN$), 4.0 (s br, 1H, NH), 3.95 (m, 1H,$CHCH_AH_BN$), 3.79 (m, 1H, $CH_AH_BOH$), 3.71 (m, 1H, CH), 3.57 (s, 1H, CH), 3.55 (s, 3H, $OCH_3$), 3.44 (dd, 1H, $J$ = 10.9, 2.5 Hz, $CH_AH_BOH$), 3.41 (s, 3H, $OCH_3$), 3.15 (m, 1H, CH), 3.07 (dd, $J$ = 16.4, 3.4Hz, $CH_AH_BCHN$), 2.52 (dd, $J$ = 15.3, 4.1Hz, $CH_AH_BCHN$), 2.46 (s, 3H, $NCH_3$), 2.43 (m, 1H, $CH_AH_BCHN$), 2.2 (m, 1H, $CH_AH_BCHN$), 2.14 (s, 3H, $CH_3$), 2.08 (s, 3H, $CH_3$). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 168.8 (NCO), 168.0 (NCO), 151.0 (ArC), 150.8 (ArC), 145.9 (ArC), 143.6 (ArC), 139.4 (2ArC), 139.3 (ArC), 133.9 (Ar*C*H), 133.5 (Ar*C*H), 131.9 (2ArC), 123.3 (Ar*C*H), 123.1 (Ar*C*H), 120.9 (Ar*C*H), 120.8 (ArC), 120.7 (ArC), 112.2 (ArC), 112.1 (ArC), 101.0 ($OCH_2O$), 64.2 (CH), 63.6 ($OCH_2$), 60.1 ($OCH_3$), 59.9 ($NCH_3$, $OCH_3$ ), 52.5 (CH), 49.0 (CH), 45.7 (CH), 39.6 ($CH_2$ ), 31.7 ($CH_2$ ), 26.6 ($CH_2$ ), 15.6 ($CH_3$), 8.9 ($CH_3$). ESI-MS: *m/z* (%) = 616 $[M + H]^+$ (100), 617 $[M + 2H]^+$ (35). HRMS (EI) calcd for $C_{34}H_{38}O_8N_3$ $[M]^+$ 616.2659, found 616.2659.

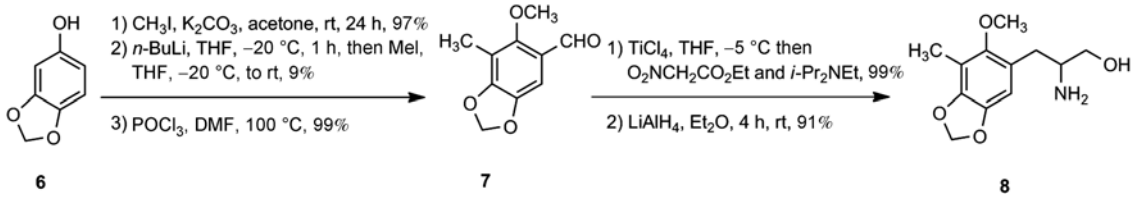
*Phthalascidin 622 (**4**)*

DMSO (571 mg, 7.32 mmol) was added to the stirring solution of $(COCl)_2$ (929 mg, 7.32 mmol) in DCM (20 mL), at −60 °C. After stirring for 30 min, the amine 20 (150 mg, 0.244 mL) dissolved in DCM (6 mL) was added at −60 °C. Then the reaction mixture was stirred for an additional time of 30 min at −60 °C and *i*-$Pr_2$NEt (1.6 g, 12.19 mmol) was added. The mixture was stirred for 1h at room temperature and TMSCN (474 mg, 4.78 mmol) was added dropwise. After stirring overnight at room temperature, the reaction mixture was washed with water (3 × 50 mL) and brine, dried over $Na_2SO_4$, filtered, evaporated and purified by flash column chromatography ($SiO_2$, cyclohexane/AcOEt 100:00 → 00:100 then MeOH) to yield the phenol 4 as a brown solid (40 mg, 27%). $R_f$ = 0.3 (DCM/MeOH = 86:14). $^1$H NMR ($CDCl_3$ , 500 MHz) $\delta$ 7.73 (m, 2H, 2ArH), 7.68 (m, 2H, 2ArH), 6.41 (s, 1H, $ArH_{15}$), 5.75 (s, 1H, ArOH), 5.54 (s, 1H, $OCH_AH_BO$), 5.04 (s, 1H, $OCH_AH_BO$), 4.23 (s, 1H, $H_{12}$), 4.19(d, 1H, $J$ = 8.2 Hz, $H_1$), 4.11 (s, 1H, $H_{11}$), 3.74 (s, 3H, $OMe_{17}$), 3,71 (s, 3H, $OMe_5$), 3.60 (m, 2H, $H_{22}$ and $H_{22'}$), 3.36 (d, 1H, $J$ = 7.5 Hz, $H_{13}$), 3.21 (m, 2H, $H_3$ and $H_{4'}$), 3.07 (dd, 1H, $J$ = 7.6, 18.1 Hz, $H_{14'}$), 2.62 (d, 1H, $J$ = 19.9 Hz, $H_{14}$), 2.31 (s, 3H, NMe), 2.24 (s, 3H, $Me_{16}$) 2.08 (s, 3H, $Me_6$), 1.84 (m, 1H, $H_4$). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 168.4 (2N*C*O), 150.4(Ar*C*O$Me_1$), 146.9 (Ar*C*OH), 144.5 (Ar*C*O), 142.9 (Ar*C*O$Me_2$), 139.8 (Ar*C*O), 134.1 (2Ar*C*H), 132.3 (2Ar*C*), 131.3 (Ar*C*), 128.9 (Ar*C*) , 123.5 (2Ar*C*H), 121.3 (Ar*C*), 121.2 (Ar*C*H), 118.7 (CN), 116.9 (Ar*C*), 113.9 (Ar*C*) 112.6 (Ar*C*), 101.2 (O*C*$H_2$O), 61.4 (OMe), 61.1 (OMe), 61.0 (*C*H), 58.1 (*C*H), 57.0 (*C*$H_2$), 55.9 (*C*$H_3$), 55.6 (*C*H), 42.9 (*C*$H_2$), 42.2 (NMe), 26.5 (*C*$H_2$), 25.9 (*C*$H_2$), 16.4 (Me), 9.7 (Me). ESI-MS: *m/z* (%) = 623 $[M + H]^+$ (100), 624 $[M + 2H]^+$ (33). HRMS (EI) calcd for $C_{35}H_{35}O_7N_4$ $[M]^+$ 623.2506, found. 623.2510.

## 3 Results and discussion

N-protected α-amino-alcohol **13** was obtained from the aminoalcohol **8**. Starting from the commercially available sesamol **6**, methylation of the hydroxyl group with MeI in a suspension of $K_2CO_3$ in acetone as a base followed by a selective *ortho*-lithiation in THF using *n*-BuLi at −20 °C, and methylation with MeI, allowed the formation of the corresponding methylated intermediate in 86% yield over two steps. The Vilsmeier-Haack formylation of this derivative with $POCl_3$ in DMF at 100 °C gave rise to aldehyde **7**, which was purified by recrystallisation in 99% yield [42]. Aldehyde **7** was then engaged in a Knoevenagel condensation with ethyl nitroacetate in THF, in the presence of $TiCl_4$ and *i*-$Pr_2$NEt, to afford the corresponding nitroalkene in 99% yield as a 1:1 mixture of *E*/*Z* isomers [43–45]. Then, the simultaneous reduction of the carbon-carbon double bond, ester and nitro functions was accomplished by $LiAlH_4$ in $Et_2O$ in 91% yield, giving the racemic α-amino-alcohol **8** used in the next step without further purification. Compound **8** was obtained in 77% overall yield after five synthetic steps, with only two silica gel chromatography purification.

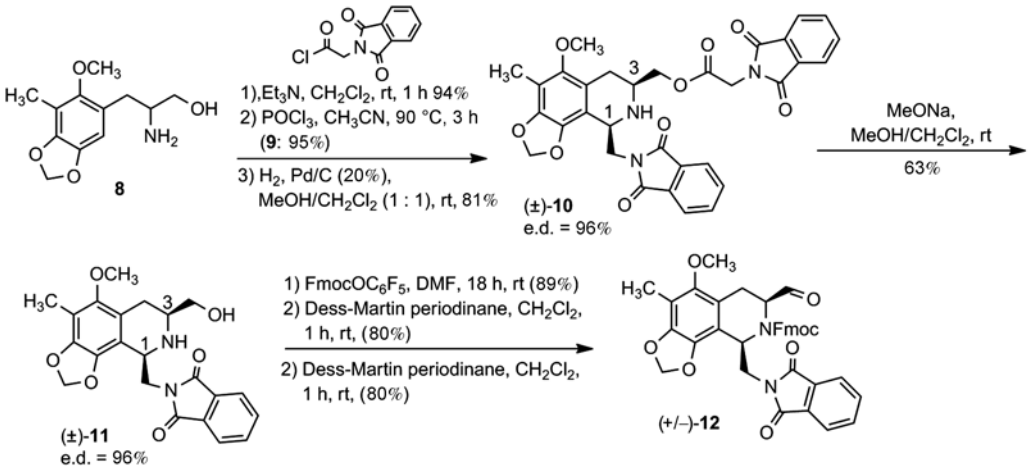
Acylation of both alcohol and amine reactive sites of **8** with phthaloyl glycine chloride [46, 47] in $CH_2Cl_2$, in the presence of $NEt_3$, provided the corresponding diprotected intermediate. The latter was then converted into the corresponding



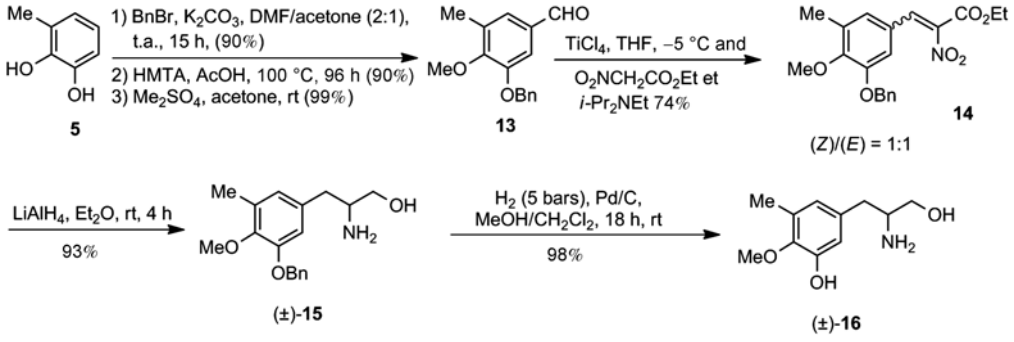

**Scheme 1** Synthesis of α-amino-alcool **8**.

tetrahydroisoquinoline **10** through a Bischler-Napieralski reaction with $POCl_3$ in DMF which proceeded in 95% yield [48, 49], followed by a highly diastereoselective hydrogenation of the dihydroisoquinoline **9**. Indeed, reduction of the imine function by $H_2$ in the presence of 20% Pd/C in a 1:1 mixture of MeOH/$CH_2Cl_2$ proceeded smoothly, to give racemic α-amino-ester *cis*-**10** in 81% yield with a diastereoisomeric excess of 96%, determined by $^1$H NMR of the crude reaction mixture. The α-amino-ester *cis*-**10** was then transesterified in a 1:1 mixture of MeOH/$CH_2Cl_2$ in the presence of MeONa, providing the α-amino-alcohol *cis*-**11** in 63% yield. The *cis*-configuration of **11** was determined on the basis of the 500 MHz NOESY spectrum analysis from the correlation analysis of the cross peak protons between H-1 and H-3. The amino group of (±)-**11** was consequently protected with 9-fluorenylmethyl pentafluorophenyl carbonate in DMF, affording the corresponding *N*-protected α-amino-alcohol in 89% yield. Subsequent oxidation of the hydroxyl group of this derivative in the presence of Dess-Martin periodinane reagent [50, 51] in $CH_2Cl_2$ gave rise to the formation of the chemically stable aldehyde (±)-**12** in 80% yield [38].

Then, we focused on the synthesis of a phenolic α-amino-alcohol synthetic precursor **16** (Scheme 3) which could be readily accessible and compatible for the stereoselectivity and regioselectivity of the Pictet-Spengler cyclization [25, 52, 53]. The synthesis of phenolic α-amino-alcohol **16** has been conducted in 6 steps of classical chemical transformations with an overall yield of 57%. Regioselective benzylation of the less hindered hydroxyl group of the commercially available 3-methylcatechol **5**, followed by Duff formylation




**Scheme 2** Synthesis of *N*-protected α-amino-aldehyde **12**.



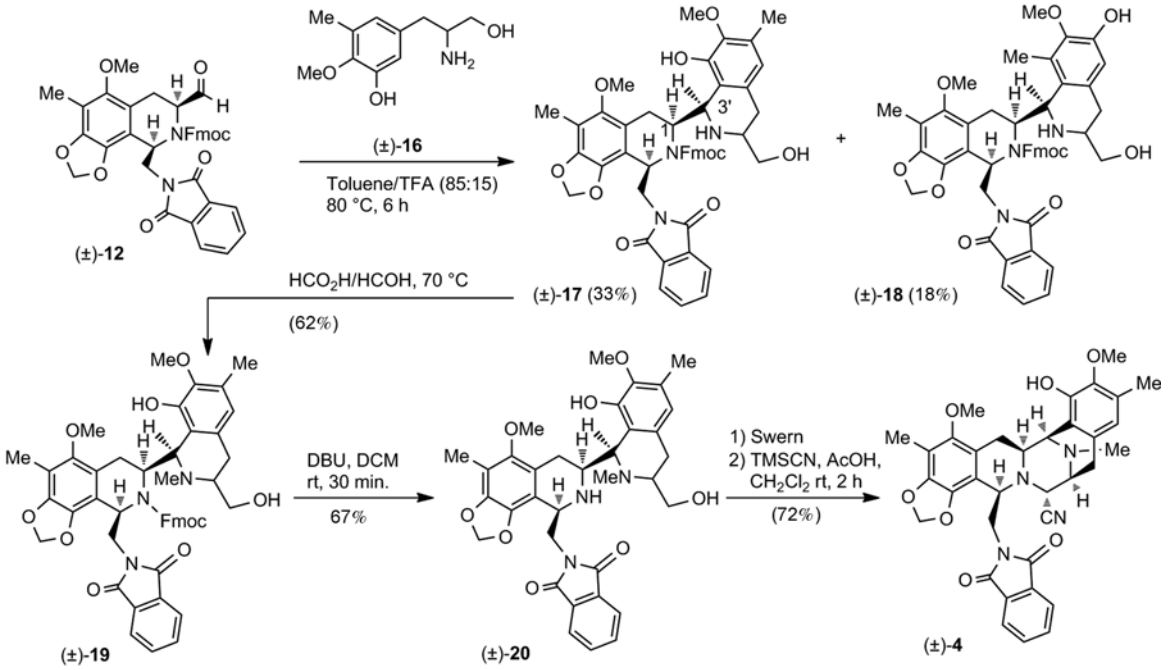

**Scheme 3** Synthesis of phenolic α-amino-alcohol **16**.

[54, 55] and *O*-methylation of the residual hydroxy group gave **13** in a 85% global yield. Knoevenagel condensation [43] of **13** with ethyl nitroacetate gave **14** in a 1:1 mixture of *E*/*Z* nitroketene derivative. Compound **14** was then reduced with $LiAlH_4$ to afford the corresponding racemic α-amino-alcohol **15** in 93% yield. Finally, hydrogenolysis of the benzyl group of **15** was realized in presence of Pd/C under 5 bar of $H_2$ in a 1:1 mixture of $MeOH/CH_2Cl_2$, to obtain the corresponding phenol **16** in 98% yield.

The iminobenzazocine pentacyclic system **21** was finally obtained in four steps from the preliminary Pictet-Spengler condensation of the diastereoisomer **12** with the racemic amino-alcohol **16** (Scheme 4). Cyclisation was performed at 80 °C in a 85:15 mixture of toluene/TFA [56, 57] to give a mixture of (1, 3′)-bistetrahydroisoquinolines as two regioisomers **17** and **18**, respectively in 33% and 18% yields. The regisomer **17** arised from cyclization *otho*- to the 3-phenolic group of **16**, and **18** from cyclization *para*- to the same 3-phenolic group. The complete stereochemical assignments of (1,3′)-bistetrahydroisoquinolines was achieved by NMR. Structural elucidation of **17** and **18** was made by 2D NMR (HSQC, COSY, HMBC and NOESY techniques). Moreover, **17** and **18** were obtained as mixtures of two diastereoisomers. The *cis* configuration of diastereoisomers **17** and **18** was determined on the basis of the 500 MHz NOESY spectrum analysis from a correlation analysis of the cross-peak protons between H-1 and H-3′. After methylation of the secondary amine of **17** in the Escweiler Clarke conditions ($HCO_2H$/HCOH, 2:1.7), the cleavage of the *N*-Fmoc group of **19** occurred by treatment with DBU affording the amine **20** in 67% yield. Finally, **4** was obtained in 72% yield by an intramolecular Stecker reaction based on the Swern oxidation of the primary alcohol of **20** followed the treatment of the corresponding hemiaminal formed *in situ* with TMSCN.

High-resolution EIMS of (±)-phtalascidin 622 4 demonstrated a molecular composition of $C_{35}H_{35}O_7N_4$ $(M+H)^+$ by observation of the peak at a *m/z* 623.2510 (Δ–0.4 mmu). The lack of published data for 4 frustrated our attempts to identify our sample by simple comparison of NMR data. Therefore, extensive analyses of spectral data were necessary to confirm the structure. All protons and carbons were assigned by NMR experiments including COSY, HSQC, HMBC and NOESY techniques (Figures 3 and 4).

More especially, the resonance signal of the residual aromatic proton $H_{15}$ was located at 6.41 ppm based on the cross peaking correlation with $H_{14}$, $H_{14'}$ and $Me_{16}$ resonance signals identified from the COSY and NOESY spectra and located at 2.24 ppm, 2.62 ppm and 3.07 ppm respectively. From these hypotheses, $OMe_{17}$ was characterized by a singlet at 3.74 ppm which was confirmed by a NOESY cross peaking correlation with the OH group at 5.75 ppm. COSY experiment allowed us to assign all of the resonance signals to the corresponding protons and the proposed stereochemistry of 4 was confirmed by NOESY experiment, especially for the *cis* position of $H_4$, $H_3$ and $H_{11}$ as well as the *anti* position of $H_{12}$ towards $H_1$ and $H_{13}$ which is also in *anti* with $H_{14'}$. HSQC experiment allowed us to attribute all of the primary, secondary and tertiary carbons. Finally, resonance signals of the quaternary carbons were deduced from the HMBC experiment.




**Scheme 4** Synthesis of (±)-Pt 622 **4**.

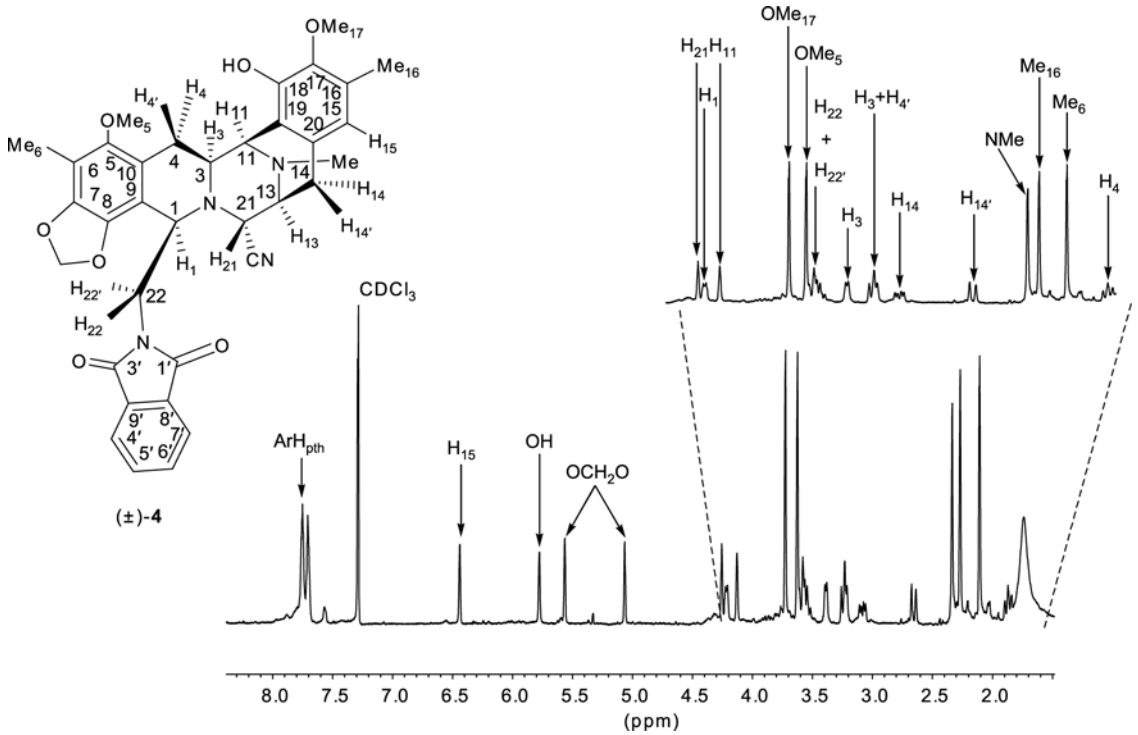



**Figure 3** $^{1}$H NMR spectrum of **4** ($CDCl_3$).

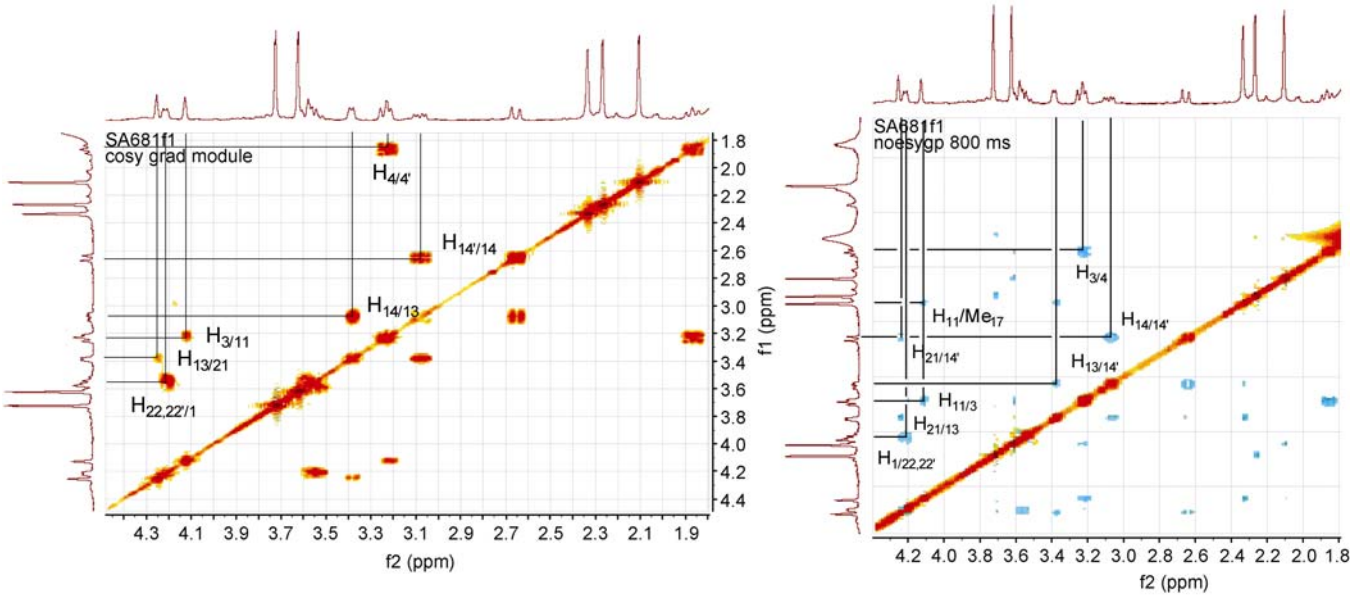



**Figure 4** 2D COSY and NOESY spectra of **4** ($CDCl_3$).

## 4 Conclusion

To conclude, a practical synthesis of fully functionalized phenolic α-amino-alcohol (±)-**16** which constitutes the catechol aromatic fragment of the tetrahydroisoquinoline of (±)-Pt 622, has been synthesized in six steps from 3-methyl catechol **5** with an overall yield of 57%. After four additional steps involving a Pictet-Spengler condensation from the synthetic precursors (±)-**12** and (±)-**16**, Pt 622 4 was finally obtained in an overall yield of 5.6%.

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